"Perspectives on the Properties of Stem Cells" (2005), by Ernest McCulloch and James Till [1]

By: Bains, Ajeet Keywords: Stem cells [2] Coloney Forming Cells [3] Stem Cell Properties [4]

In 2005, Ernest McCulloch and James Till published the article "Perspectives on the Properties of Stem Cells," which discusses the various properties and future possibilities for the use of stem cells [5]. Stem cells are unspecialized cells that can develop into several different cell types. In the article published in the journal Nature on 1 October 2005, the authors say they wrote the article to dispel misconceptions about what stem cells [5] are, what they do, address some controversies surrounding stem cells [5], and discuss potential uses of stem cells [5]. In the article, McCulloch and Till reveal how stem cell research has revolutionized cancer treatment as well as set the stage for future embryonic and adult stem cell research.

Stem cells are cells with the potential to develop into different types of cells. They are different from other cells in that they are not specialized and can divide and renew themselves over a long span of time. Because stem cells [5] are not specialized, they cannot perform specific functions in the body. However, they have the potential to become specialized cells, such as muscle, blood, and nerve cells [6]. The two main types of stem cells [5] are embryonic stem cells [7] and adult stem cells [8]. Adult stem cells [5] are multipotent, so they give rise to a certain number of varied cell types, but embryonic stem cells [7] are pluripotent and can give rise to any cell type. Adult stem cells [5] are more specialized than embryonic stem cells [7], and they can remain in a non-specialized state until the body needs to repair or grow new tissue. Embryonic stem cells [5] are stem cells [5] in the undifferentiated cells in an embryo. Embryonic stem cells [5] can replicate many more times than adult stem cells [8] and give rise to more than 200 cell types in the body.

Known for their pioneering role in stem cell research, Ernest McCulloch, studied blood and blood diseases, and James Till, studied the effects of radiation [9] on cell development. From 1958 to 1963 McCulloch and Till worked at the Ontario Cancer Institute, with spleens from irradiated mice, and their research supported the hypothesis that cells have the ability to self-renew, divide, and differentiate. Bone marrow cells are immature blood cells that differentiate in to the functioning blood cells that circulate through the body. When McCulloch and Till transplanted bone marrow cells into lethally irradiated mice, they noticed small lumps on the mice's spleens. They later concluded that the lumps were clones of cells arising from a single cell, now called a stem cell. The authors' finding provided the foundation for research on physically isolating stem cells [5], studying their characteristics, and developing them for medical use. It also enabled the pursuit of other types of stem cells [5], including embryonic stem cells [7].

McCulloch and Till's article has an introduction and three main sections. In the first section "An early example of stem cell diversity," McCulloch and Till discuss their experiment with the spleens from irradiated mice and how they speculated that the colonies that formed on the mouse [10] spleens during their experiment were due to stem cell division. In the second section "Some Current Issues in Stem Cell Biology," the authors discuss how the plasticity of stem cells [5] remains controversial as well as how stem cell activity accelerates the growth of cancer in the human body. In the final section: "Why now? Possibilities and Controversies" the authors discuss the many applications of stem cells [5] to regenerative medicine [11] along with the large amount of publicity stem cells [5] received in 2005 and still in 2019.

The article begins by discussing the definition of a stem cell along with stem cell properties. McCulloch and Till define stem cells [5] as undifferentiated cells that retain the ability to differentiate into other cell types, which allows them to act as a repair system for the body by replenishing other cells. However, the authors claim that the popular definition, which appeared in numerous anatomy books in the early 2000s, oversimplifies the wide range of stem cell properties. According to the authors, the definition gives rise to misconceptions that stem cells [5] are simply undifferentiated cells that can give rise to differentiated descendants or that stem cell descendants do not retain stem cell properties. The common definition also ignores self-renewal, where stem cells [5] are capable of producing new stem cells [5]. However, some progeny of stem cells [5] lose the ability for self-renewal and differentiate or begin terminal cell divisions, which lead to the formation of tissues and organs. Finally, the concept of plasticity challenges the simplicity of the common definition. Plasticity is the ability of adult tissue-specific stem cells [5] to develop into new types of cells of other tissues. For example, hematopoietic, or blood, stem cells [5] under certain conditions can give rise to liver, muscle, and brain cells. Plasticity gives stem cells [5] a wide range of use in medicine with functional applications in cancer treatment and regenerative medicine [11].

In the next section, "An early example of stem cell diversity," the authors describe the experiments in which they discovered some cells that could self-renew. In 1961, McCulloch and Till were working on determining how sensitive mouse [10] bone marrow cells were to radiation [9]. In the course of those experiments, they noticed colonies of unusual cells growing in the spleens of irradiated mice. The authors tested the cells in the colonies and found that some of the cells were able to create new

colonies. In other words, the authors found that those cells could self-renew. The authors published the findings in a 1963 article that showed that each of the colonies from a single cell, the cells in the spleen colonies could self-renew, dividing to form, new colony-forming cells.

Continuing on in their discussion of early stem cell research, McCulloch and Till discuss an observation by Louis Siminovitch in 1963 that new colony-forming cells were distributed unevenly throughout the colonies. A few colonies contained large numbers of new colony-forming cells, but the majority of colonies contained much smaller numbers. One explanation for that was the heterogeneity developed during the formation of a colony. The authors developed a model of how colonies formed in order to determine why the new colony-forming cells were unevenly scattered. Their work provided a basis for how stem cells [5] develop and continually maintain the overall number of stem cells [5] in order to renew tissues within an animal's body. The authors state that two factors controlled how many stem cells [5] were in the colonies. The first was how many newstem cells [5] were produced by self-renewal, and the second was how many stem cells [5] the colony lost by either specialization or cell death. McCulloch and Till designed their model so that whether a stem cell would self-renew or become lost was random, similar to how radioactive atomic nuclei behave. Scientists can predict when a group of nuclei will decay, but they cannot predict exactly when a specific nucleus [12] will decay. The authors applied that same principle to understand howstem cells [5] behaved.

The second section "Some Current Issues in Stem Cell Biology," has sub-sections. In the "Plasticity," sub section the authors move into a discussion of how scientists questioned the nature of stem cells [5] after the discovery of their plasticity. McCulloch and Till note that scientists explained that stem cells [5] functioned only in systems that depended on constant cell renewal and differentiation [13] such as in blood and skin cells. Other body systems respond to injury by divisions in cells that have already differentiated. For example, after a partial surgical removal of the liver mature liver cells divide and replace the functional of the removed section. The discovery of stem cells [5] that give rise to blood cells can also in certain circumstances give rise to liver, muscle and brain cells challenged those ideas.

In addition, subsets of cells from those organs can repopulate blood and bone marrow. According to the authors, the plasticity of stem cells [5] remains a subject of future study. If adult stem cells [8] that have the potential to differentiate and produce the functional cells of several organs do exist, then such cells might well be targets for carcinogenic events. Because a characteristic of cancer is uncontrolled cell growth, plastic stem cells [5] that begin dividing uncontrollably may give rise to cancerous tumors.

In the sub-section "Cancer," the authors discuss the application ofstem cells [5] to cancer treatment. Cancer is a disease in which abnormal cells divide without control and can invade nearby tissues. Most types of cancer derive from a single cancer stem cell, and the descendants of those cells are clones. The clones contain newly formed cancer stem cells [5] and malignant appearing cells that cannot continuously multiply. Thus, the development and continuous growth of cancers depend on the activity of stem cells [5]. Stem cells are the targets for effective cancer therapy. Cancers vary greatly in their cellular composition; their behavior, growth and response to treatment reflect the variation in composition. It is a goal of many cancer researches to develop methods that measure variation and relate the measurements to outcome. Many techniques developed, the most valuable are ones that measure either stem cell number or a crucial property of the stem cells [5] of a particular tumor.

McCulloch and Till in the final section, "Why now? Possibilities and Controversies,"discuss how an extensive amount research has led to the identification of various categories of stem cells [5]. Stem cells that ranging from the union of thesperm [14] and egg [15] cell to form the totipotent zygote [16] able to develop in to any cell in the body to the multipotent adult stem cell. The authors suspect that in the future, embryonic stem cells [7] could provide a way to regenerate damaged organs, such as the heart and brain. However, due to the publicity that stem cells [5] have received, the authors describe major controversies that occurred over how best to regulate research on stem cells [5]. For example, when researchers cloned Dolly thesheep [17], the public questioned whether the same cloning [18] technique could clone people. For future research, the authors indicate an important question that stem cell scientists ask is how many mature bone marrow cells have the ability to transform into other cells types as observed with embryonic stem cells [7].

McCulloch and Till's research provided the first functional identification of a stem cell of the blood-forming system, and their discovery set the stage for subsequent research on adult and embryonic stem cells [7]. In particular, the authors' article provided essential information that researchers of cancer therapeutics have used.

Several cancer studies published within a few years of the articles publication cite this article. Those studies analyze the properties of stem-like cells in tumors and determine how these stem-like cells can act as targets for therapeutic treatment. McCulloch and Till's article provides essential information about the properties of stem cells [5], and their article serves as a foundation for future research on how stem cells [5] can be altered or targeted for medical purposes.

Sources

1. Becker, Alexander; Ernest A. McCulloch, and James E. Till, "Cytological Demonstration of the Clonal Nature of Spleen Colonies Derived from Transplanted Mouse Marrow Cells." *Nature* 197 (1963): 452–4. http://www.jimmunol.org/content/jimmunol/192/11/4945.full.pdf [19] (Accessed March 19, 2019).

2. Clarke, Michael F. and Andrew T. Hass, "Cancer Stem Cells." In*Reviews in Cell Biology and Molecular Medicine*, R. A. Meyers, ed. Wiley Online Library, 2006.
3. Kuehn, Bridget, and Tracy Hampton. "2005 Lasker Awards Honor Groundbreaking Biomedical Research, Public Service." *Journal of the American Medical Association* [20]., 294 (2005), 1327–30.
4. Mayo Clinic Staff. "Stem Cells: What They Are and What They Do."*Mayo Foundation for Medical Education and Research*, March 23, 2013 updated July 23, 2018. https://www.mayoclinic.org/tests-procedures/stem-cell-transplant/in-depth/stem-cells/ART-20048117?p=1 [21] (Accessed March 5, 2019).
5. McCulloch, Ernest A. and James E. Till. "Perspectives on the Properties of Stem Cells."*Nature Medicine* 11 (2005): 1026–8. https://www.scirp.org/journal/PaperInformation.aspx?paperID=44773 [22] (Accessed February 18, 2019).
6. Siminovitch, Louis, Ernest A. McCulloch, and James E. Till, "The Distribution of Colony-forming Cells Among Spleen Colonies" *Journal of Cellular and Comparative Physiology*62 (1963): 327–36. https://tspace.library.utoronto.ca/bitstream/1807/2778/2/JCP_1963_62_327.pdf [23] (Accessed March 19, 2019).
7. Till, James E. and Ernest A. McCuloch, "A Direct Measurement of the Radiation Sensitivity of Normal Mouse Bone Marrow Cells." *Radiation Research*, 14 (1961): 213–22.https://tspace.library.utoronto.ca/retrieve/4606/RadRes_1961_14_213.pdf [24] (Accessed March 19, (Accessed March 19, 2019).

In 2005, Ernest McCulloch and James Till published the article “Perspectives on the Properties of Stem Cells,” which discusses the various properties and future possibilities for the use of stem cells. Stem cells are unspecialized cells that can develop into several different cell types. In the article published in the journal Nature on 1 October 2005, the authors say they wrote the article to dispel misconceptions about what stem cells are, what they do, address some controversies surrounding stem cells, and discuss potential uses of stem cells. In the article, McCulloch and Till reveal how stem cell research has revolutionized cancer treatment as well as set the stage for future embryonic and adult stem cell research.

Subject

Stem cells [25] embryonic stem cells [26] Bone marrow Stem Cells [27] Somatic Stem Cells [28] Stem cells--Research [29] Adult stem cells [30] Properties of Stem Cells [31] Hematopoietic stem cells [32] Multipotent stem cells [33] Bone Marrow Cells [34] Stem Cells [35] Adult Stem Cells [36] Colony-Forming Units [37] Cell Differentiation [38] Cell Self Renewal [39] Embryonic Stem Cells [40] Progenitor Cells [41] Cell Self Renewal [39]

Topic

Publications [42]

Publisher

Arizona State University. School of Life Sciences. Center for Biology and Society. Embryo Project Encyclopedia.

Rights

Format

Articles [43]

Last Modified

Wednesday, July 1, 2020 - 00:13

DC Date Accessioned

Wednesday, July 1, 2020 - 00:07

DC Date Available

Wednesday, July 1, 2020 - 00:07

DC Date Created

2020-06-30

- The Embryo Project at Arizona State University, 1711 South Rural Road, Tempe Arizona 85287, United States

---

. . .

Links
[1] https://embryo.asu.edu/pages/perspectives-properties-stem-cells-2005-ernest-mcculloch-and-james-till
[2] https://embryo.asu.edu/keywords/stem-cells
[3] https://embryo.asu.edu/keywords/coloney-forming-cells
[4] https://embryo.asu.edu/keywords/stem-cell-properties
[5] https://embryo.asu.edu/search?text=stem%20cells
[6] https://embryo.asu.edu/search?text=nerve%20cells
[7] https://embryo.asu.edu/search?text=embryonic%20stem%20cells
[8] https://embryo.asu.edu/search?text=adult%20stem%20cells
[9] https://embryo.asu.edu/search?text=radiation
[10] https://embryo.asu.edu/search?text=mouse
[11] https://embryo.asu.edu/search?text=regenerative%20medicine
[12] https://embryo.asu.edu/search?text=nucleus
[13] https://embryo.asu.edu/search?text=differentiation
[14] https://embryo.asu.edu/search?text=sperm
[15] https://embryo.asu.edu/search?text=egg
[16] https://embryo.asu.edu/search?text=zygote
[17] https://embryo.asu.edu/search?text=sheep
[18] https://embryo.asu.edu/search?text=cloning
[19] http://www.jimmunol.org/content/jimmunol/192/11/4945.full.pdf
[20] https://embryo.asu.edu/search?text=American%20Medical%20Association
[21] https://www.mayoclinic.org/tests-procedures/stem-cell-transplant/in-depth/stem-cells/ART-20048117?p=1
[22] https://www.scirp.org/journal/PaperInformation.aspx?paperID=44773
[23] https://tspace.library.utoronto.ca/bitstream/1807/2778/2/JCP_1963_62_327.pdf
[24] https://tspace.library.utoronto.ca/retrieve/4606/RadRes_1961_14_213.pdf
[25] https://embryo.asu.edu/library-congress-subject-headings/stem-cells-0
[26] https://embryo.asu.edu/library-congress-subject-headings/embryonic-stem-cells
[27] https://embryo.asu.edu/library-congress-subject-headings/bone-marrow-stem-cells
[28] https://embryo.asu.edu/library-congress-subject-headings/somatic-stem-cells
[29] https://embryo.asu.edu/library-congress-subject-headings/stem-cells-research
[30] https://embryo.asu.edu/library-congress-subject-headings/adult-stem-cells
[31] https://embryo.asu.edu/library-congress-subject-headings/properties-stem-cells
[32] https://embryo.asu.edu/library-congress-subject-headings/hematopoietic-stem-cells
[33] https://embryo.asu.edu/library-congress-subject-headings/multipotent-stem-cells
[34] https://embryo.asu.edu/medical-subject-headings/bone-marrow-cells
[35] https://embryo.asu.edu/medical-subject-headings/stem-cells
[36] https://embryo.asu.edu/medical-subject-headings/adult-stem-cells
[37] https://embryo.asu.edu/medical-subject-headings/colony-forming-units
[38] https://embryo.asu.edu/medical-subject-headings/cell-differentiation
[39] https://embryo.asu.edu/medical-subject-headings/cell-self-renewal
[40] https://embryo.asu.edu/medical-subject-headings/embryonic-stem-cells
[41] https://embryo.asu.edu/medical-subject-headings/progenitor-cells
[42] https://embryo.asu.edu/topics/publications
[43] https://embryo.asu.edu/formats/articles